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Bilirubin and protein concentration in cord blood after spontaneous versus induced labor. Correlation to neonatal hyperbilirubinemia.

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1 Introduction

The correlation between oxytocin administration for induction or augmentation of labor and neonatal jaundice is still a matter of debate. In a controlled retrospective study [4] the incidence of neonatal jaundice after oxytocin administration was 12.4 per cent as compared to 8.1 per cent in a control group. BEAZLEY and ALDERMAN [2] have found a significant association between the mean total dose of oxytocin used for induction and the incidence of neonatal hyperbilirubinemia, suggesting a dose-dependent response. On the other hand GOULD et al. [11] in a prospective study, failed to demonstrate an effect of maternal oxytocin infusion on neonatal serum bilirubin levels on the first and sixth days of life. SIVASURIYA et al. [20] similarly failed to find any difference in serum bilirubin levels in the first five days of life of neonates following spontaneous onset of labor and induced labor by various methods, including oxytocin infusion. A significant correlation between oxytocin administration and neonatal jaundice was claimed by DAVIES et al. [7] as being limited to artificially induced labors, and no difference was noted between spontaneous and oxytocin augmented, following spontaneous onset deliveries. The authors speculated that a relative immaturity of hepatic enzymes in the offspring of women who do not spontaneously enter parturition might be the explanation of their tendency to present with neonatal jaundice.

Curriculum vitae

M. GRANAT *was born in 1943 in Haifa, Israel. Graduated from the Medical School of the Hadassah University Hospital in Jerusalem in 1970. Residency in Obstetrics and Gynecology at the Rothschild University Hospital, Faculty of Medicine, Technion, Haifa. Acquired a Diploma in Obstetrics and Gynecology from the Postgraduate School of the Tel-Aviv University Medical School. Since 1978 – Senior Physician in the Department of Obstetrics and Gynecology of the Hadassah University Hospital in Jerusalem. Lecturer at the Medical School of the Hebrew University, Jerusalem. Main clinical and research interests are in the field of perinatal medicine, mainly prenatal diagnosis and monitoring of high risk pregnancies, and problems of blood coagulation.*

Similar findings presented by JEFFARES [13] again raised the question as to whether induction itself, rather than the effect of oxytocin might be a contributory factor in the causation of neonatal jaundice. Evidence of a dose dependent effect of oxytocin on the severity of neonatal jaundice and on the level of bilirubin in cord blood has been recently presented [8].

The widespread liberal use of oxytocin to induce or accelerate labour, often without medical necessity, inspite of the aforementioned contradictory experiences, prompted us to prospectively re-

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examine the relative role of oxytocin versus artificial induction of labor per se as alleged causes of neonatal hyperbilirubinemia.

2 Material and methods

71 consecutive full-term parturients were randomly selected for this study. All had uncomplicated pregnancies and were under no medications except iron preparations. The subjects were divided into three subgroups according to onset of labor and mode of delivery: 1) Normal vaginal delivery following spontaneous onset of labor (group I: n = 42). 2) Normal vaginal delivery following elective induction of labor by oxytocin drip (group II: n = 14). 3) Elective Cesarean section (group III: n = 15).

Tab. I summarises the data of these pregnancies including details of outcome.

All gestations were of 38 weeks duration or more, as calculated from menstrual history and ascertained by the DUBOWITZ score [9]. None of the newborn infants had any sign of RDS. Parturients who presented with a history of pathological pregnancies or liver disease and newborn infants who were growth retarded, or born with APGAR scores of less than 6 were all excluded from the study. Instrumental deliveries and labors starting after premature rupture of membranes were not included. Four pairs of twins were included: 2 in group I and 1 in each of the other groups. No difference was noted between duration or difficulty of delivery in groups I and II. All labors in group II were electively induced after confirmation of a "ripe cervix", for reasons of patients' convenience. Indications for Cesarean section (group III) were unrelated to the fetal status in the current pregnancies and included 10 women who underwent a previous Cesarean section because of contracted pelvis, 3 elderly primigravidas with suspicion of cephalo-pelvic disproportion and 2 women with a history of intracavitary myomectomy.

Immediately after expulsion, the placenta was spread with its fetal side upwards, the umbilical artery was identified and 8–10 ml of blood were drained. The blood underwent immediate centrifugation and the serum was stored at – 15 °C. Analyses were performed no more than 7 days later.

Total bilirubin was measured daily or more frequently as required in the venous blood of 38 neonates, who appeared to be jaundiced during their stay at the neonatal unit, their maximal bilirubin levels being recorded. Total protein was determined by the biuret method. Albumin was measured by the Bromcresol green method. Protein electrophoresis on cellulose acetate using Beckman instrument was also applied. Total bilirubin was measured by the MELLOY and EVELINE method.

U test (MANN-WHITNEY) was utilised to determine significance level of the difference between means of test results in the various groups. Regression analysis was applied for the correlation between total protein in cord serum and maximal values of bilirubin measured in the neonates.

Tab. I. Data of the three study groups (see text).

Group	I (n = 42)	II (n = 14)	III (n = 15)
Mode of delivery	Spontaneous vaginal	Induced Oxytocin	Elective Cesarean section
No. of infants	44	15	16
Maternal age (average)	25.5	30.3	31.4
Gestational age * weeks (average)	40.0	40.2	39.2
Gestational age ** weeks (average)	39.5	39.4	39.0
Birth weight (average)	3.137	3.274	3.100

* Based on menstrual history.
** Based on Dubowitz score.

3 Results

Individual values of total bilirubin in the serum of the umbilical artery are depicted in Fig. 1. No significant difference was found between the mean values in the three groups ($P > 0.05$). As summarized in Tab. II, mean total protein concentration in group I (normal deliveries of spontaneous onset) was higher than in groups II and III (deliveries induced by oxytocin and elective Cesarean sections; respectively). The difference between mean values in the "spontaneous onset" group and the

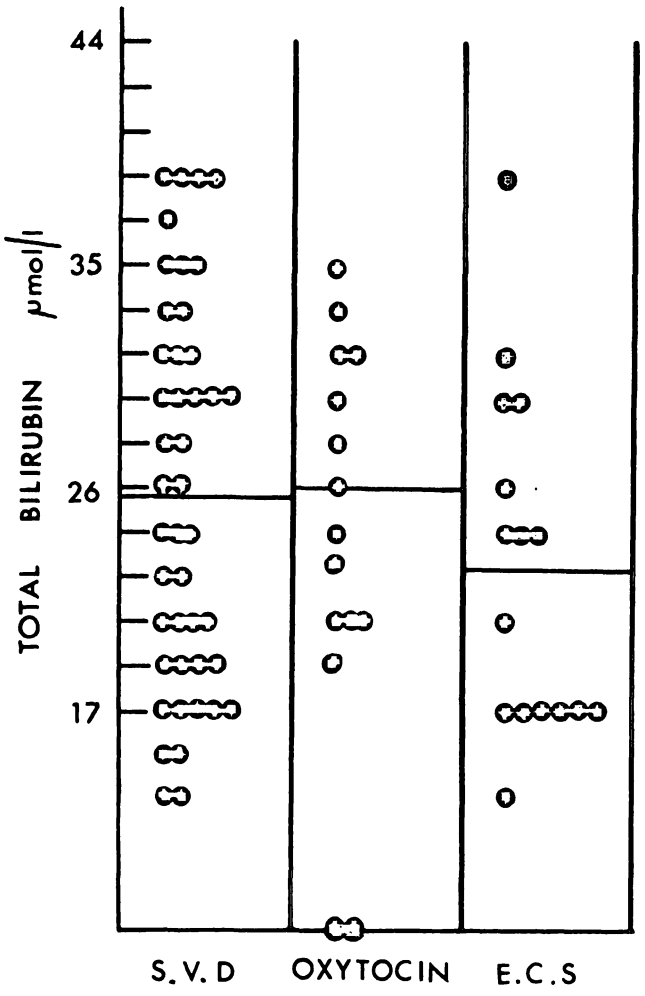

Fig. 1. Individual values of total bilirubin in cord blood in three study groups. Mean values do not differ significantly ($P > 0.05$).

S.V.D. – Vaginal delivery, spontaneous onset.
Oxytocin – Elective induction of labor by oxytocin drip, normal vaginal delivery.
E.C.S. – Elective Cesarean section.

Tab. II. Mean concentration of total protein, albumin and globulin fractions in the three study groups (Values are in gram per liter and expressed as mean ± standard error of the mean).

Group*	I	II	III
Total Protein	59 ± 6**	57 ± 6	54 ± 6**
Albumin	37 ± 30	36 ± 46	35 ± 50
α_1 Globulin	1.9 ± 7	1.7 ± 5	1.7 ± 6
α_2 Globulin	4.7 ± 12	4.5 ± 11	3.9 ± 14
β Globulin	5.5 ± 15	5.0 ± 10	4.9 ± 14
γ Globulin	10 ± 27	10.3 ± 34	8.9 ± 34

* Groups I–III as in Tab. I.
** $P < 0.05$ (Significance level of the difference between total protein concentrations in group I & III).

"elective Cesarean section" group was statistically significant ($P < 0.05$). The difference in the mean values of albumin or fractions of globulin between these groups did not reach statistical significance.

Neonatal serum bilirubin level greater than 208 μmol/liter occurred in 5 out of 15 newborn infants of the oxytocin induced group (33.3 per cent) as compared to 3 out of 44 following spontaneous-onset (6.8 per cent) and 2 out of 16 after elective Cesarean section (12.5 per cent). Clinical jaundice appeared sooner after birth in the "oxytocin induced" group as compared in the "spontaneous-onset" group and lasted longer, up to the 10th post partum day. The 2 jaundiced neonates of the "Cesarean section" group showed similar maximal values of bilirubin and duration of jaundice, but the rise was gradual, typical of "physiological jaundice". Maximal bilirubin levels in neonates who appeared jaundiced bore no significant correlation to their total protein levels in cord blood (Fig. 2).

4 Discussion

The use of oxytocin during labor has been a matter of great concern, especially in the British literature, in regard to its alleged iatrogenic effect on the occurrence of neonatal hyperbilirubinemia [2, 4, 12]. Recent studies [3, 5, 7, 11, 13, 18] cast doubt on the role of oxytocin per se in this respect, as neonatal hyperbiliruinemia seemed to occur predominantly in oxytocin induced labors as opposed to oxytocin accelerated ones following spontaneous-onset. The role of fetal hepatic maturation has been implicated in this context [7].

In this study **serum bilirubin concentration in the umbilical artery was not found to be influenced by the type of onset of labor or the route of delivery.** This is not surprising in view of the ready transfer of unconjugated bilirubin across the placenta from the fetal to maternal circulation before birth [17]. This finding apparently contradicts that of D'Souza et al. [8] who related higher doses of oxytocin to higher levels of plasma bilirubin in cord blood. However, our material is different in 2 respects: 1) The "oxytocin induced" group included only readily inducable patients who re-

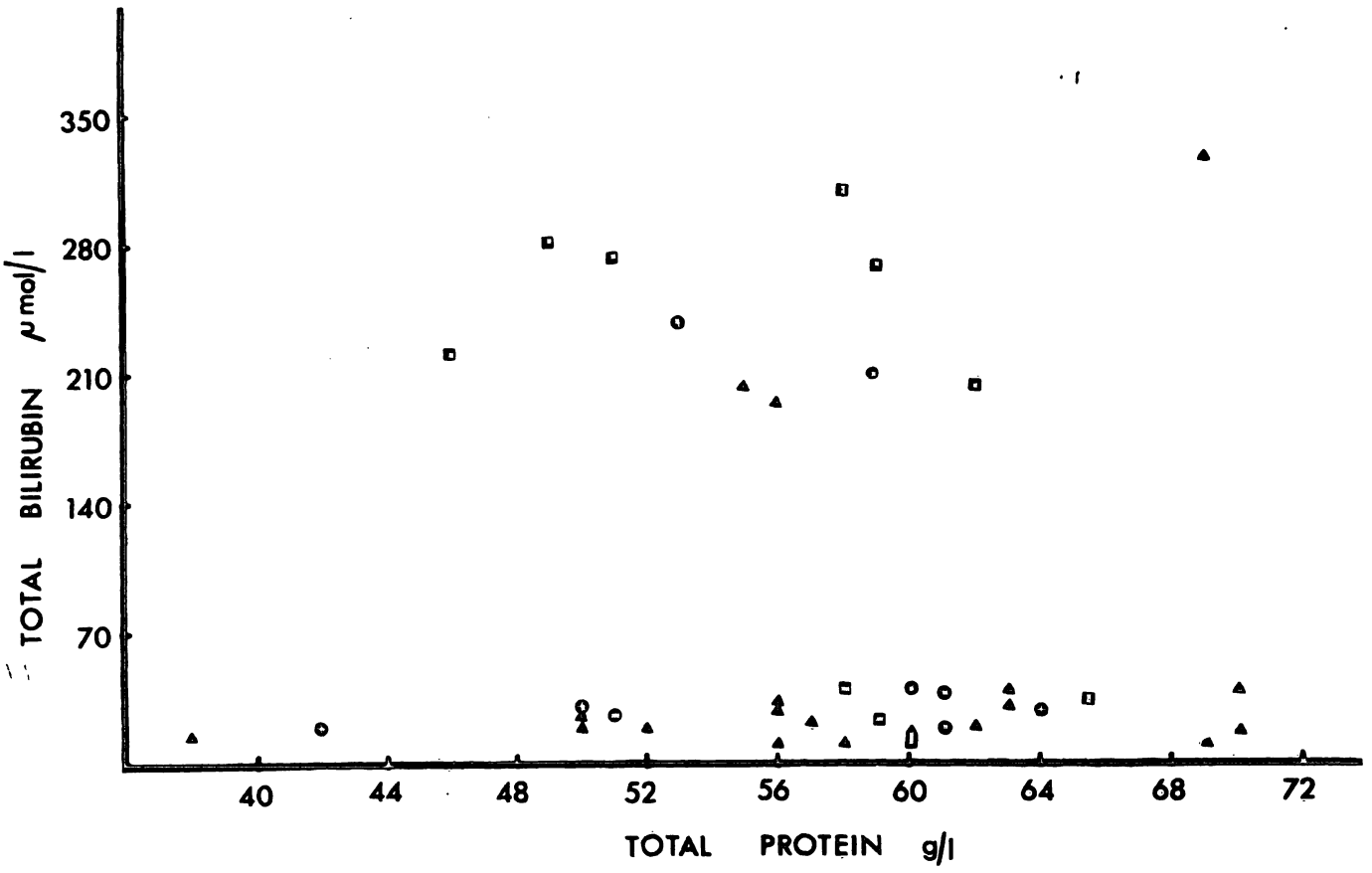

Fig. 2. Maximal Serum bilirubin levels in the neonates, versus total protein levels in the respective samples of cord blood. Correlation – not significant ($P > 0.05$).
$y = 6.925 - 0.391\ x; r = -0.048$.

▲ – Vaginal delivery; spontaneous onset.
▫ – Elective induction of labor by oxytocin drip; normal vaginal delivery.
● – Elective Cesarean section.

quired less than 3000 mu of oxytocin for the completion of labor. 2) Early amniotomy was not performed in our patients, thus presumably we have preserved the "buffer-effect" of amniotic fluid between the fetus and the uterine wall. By this we may have lessened fetal trauma and reduced the rate of red cell breakdown which was hypothesized as the cause of increased cord blood bilirubin levels that follow oxytocin induced labors [8].

Neonatal hyperbilirubinemia, however, was significantly more common following labors induced by oxytocin. No similar association was found between elective operative termination of pregnancy and neonatal jaundice, thus, conceivably, implying a direct effect of oxytocin on the causation of hyperbilirubinemia. By discarding instrumental and traumatic deliveries we could not support the suggestion recently put forward [10] that fetal-neonatal focal hemorrhages induced by difficult deliveries associated with oxytocin stimulation fully accounted for the hyperbilirubinemia.

DANCIS et al. [6] had shown that most, if not all, fetal proteins were synthesized from amino-acids in the fetal liver from as early as the third month. It appears that the concentration of albumin is not dependent upon the maternal concentration [22]. Therefore, we assumed that protein concentration in the umbilical artery could reflect maturity of the fetal liver. This assumption gains further support by the close correlation that was recently found between total protein level in cord blood and the gestational age [21]. The signifi-

cantly lower concentration of total protein that was found in the "Cesarean-section" group could be explained by the fetuses born relatively prematurely prior to the date of spontaneous onset of parturition. This might lend support to the presumptive role of fetal liver, tentatively ascribed by LIGGINS [14] and PATTEN and TURNBULL [16] to natural onset of human labour. The lack of similar difference between "spontaneous-onset" and "oxytocin induced" labors is comprehensible by the fact that the successful induction by iteself reflects a high degree of fetal maturity which is not necessarily true for the "Cesaren section" group. In a recent study [12] the mean cord plasma albumin concentration of the patients delivered by Cesarean section (37.33 g/l) was significantly less than its value following vaginal deliveries (41.97 g/l). According to MENDEHALL [15] in a mature fetus the mean albumin concentration in cord serum after elective Cesarean section was 27 gr/l. The relative immaturity of the fetal liver in the Cesarean section group, assumingly reflected by lower total protein concentration, had no significant influence on the incidence of neonatal jaundice in this group, which was relatively low. **It appears from our study, that drug effect in an as yet unidentified mechanism is responsible for the incidence of neonatal jaundice among newborn infants of oxytocin administered labors.** YAO and LIND [23] have raised the possibility of increased placental transfusion caused by narrowing of the umbilical arteries as a possible cause.

Although no serious consequences to the transient hyperbilirubinemia in the "oxytocin group" have been observed, many of them required phototherapy and needed longer hospitalization periods. This is a further disadvantage of labor induction in addition to an increased risk of an operative delivery as recently noted in a controlled study by YUDKIN et al. [24]. Therefore, **we believe that pitocin induction or augmentation should be applied only when medically indicated**, and, owing to the possibility of dose dependency, stress should be placed upon efforts to administer only the minimal effective dose.

Summary

Numerous studies have demonstrated the increased incidence of neonatal jaundice among newborns of mothers to whom oxytocin was administered during labor, the more so with induced labors. **The question as to whether the hyperbilirubinemia is the result of the induction itself, owing to relative fetal liver immaturity, versus the possibility of oxytocin drug effect is still a matter of debate.**

We attempted to shed some light on this question by measuring bilirubin and protein concentrations in cord blood and correlating the results with the occurrence of hyperbilirubinemia in the neonates. The tests were performed in 71 randomly selected full term parturients, with uncomplicated pregnancies, delivered of normal healthy infants.

The subjects were divided into 3 groups: Group I – normal vaginal delivery, following spontaneous onset of labor (n = 42); Group II – normal vaginal delivery following induction of labor by oxytocin drip (n = 14), and Group III – Elective cesarean section (n = 15). Group I and II were matched for the mean values of maternal age, gestational age at delivery and infants birthweights (Tab. I).

Blood was drawn directly from the umbilical artery and analyzed for total bilirubin and total protein. Protein electrophoresis was also applied. Total bilirubin was measured at least daily in the venous blood of 38 neonates who appeared jaundiced during their stay at the neonatal unit.

No significant difference was found between the mean values of total bilirubin in the serum of the umbilical artery in the three groups. Mean total protein concentration was, however, higher in Group I than in Groups II and III, the difference between groups I and III being statistically significant ($P < 0.05$). Neonatal serum bilirubin level greater than 208 μmol/liter occurred in 33.3 per cent of the oxytocin group (Group II) as compared to only 6.8 per cent and 12.5 per cent in Groups I and III, respectively. Maximal bilirubin levels in neonates who appeared jaundiced bore no significant correlation to their total protein levels in cord blood (Fig. 2).

The lack of correlation between serum bilirubin concentration in the umbilical artery and the type of onset of labor and route of delivery is conceivable in view of the ready transfer of unconjugated bilirubin across the placenta from the fetal to maternal circulation before birth. The significantly lower concentration of total protein that was found in the "Cesarean section group" could be explained by the relative immaturity of the fetuses born prior to the date of spontaneous onset of parturition. The easiness of successful induction of labor in the "oxytocin group" may implicate fetal maturity comparable to that found in the "spontaneous onset group", as reflected by similar total protein levels in these groups. In spite of this, neonatal hyperbilirubinemia was significantly more common following labors induced by oxytocin.

No similar association was found between elective opera-

tive termination of pregnancy and neonatal jaundice, thus apparently invalidating the concept of fetal immaturity in this context, and implying a direct effect of oxytocin on the causation of hyperbilirubinemia.
It appears from our study that **drug effect in an as yet unidentified mechanism is responsible for the increased incidence of neonatal jaundice among newborn infants of oxytocin induced labors,** with ensuing longer hospilization periods.
It is concluded that oxytocin administration should be applied only when medically indicated, and owing to the possibility of dose dependency, the minimal effective dose should be used.

Keywords: Cord blood, hyperbilirubinemia, induction of labour, neonatal jaundice, oxytocin.

Zusammenfassung

Bilirubin- und Proteinkonzentration im Nabelschnurblut nach spontanen bzw. induzierten Wehen – Korrelation zur neonatalen Hyperbilirubinämie
In zahlreichen Veröffentlichungen wird auf das gehäufte Auftreten von neonataler Gelbsucht nach Ocytocingabe an die Mutter zur Verstärkung bzw. Auslösung der Wehen hingewiesen. **Die Frage ist nun, ob die Hyperbilirubinämie Ausdruck einer relativen Leberunreife ist oder ein direkter Effekt des Pharmakons vorliegt.**
Zur Untersuchung dieser Fragestellung bestimmten wir die Bilirubin- und Proteinkonzentrationen im Nabelschnurblut und korrelierten die Werte mit dem Auftreten von Hyperbilirubinämien bei den Neugeborenen. Der Test wurde an einer randomisierten Stichprobe von 71 Gebärenden am Termin durchgeführt, die eine unkomplizierte Schwangerschaft hinter sich hatten und von gesunden Kindern entbunden wurden.
Es wurden 3 Gruppen gebildet: Gruppe I – normale vaginale Entbindung nach spontanem Einsetzen der Wehen (n = 42), Gruppe II – normale vaginale Entbindung nach Weheninduktion durch den Ocytocintropf (n = 14), Gruppe III – bestimmte Sectiones (n = 15). In den Gruppen I und II wurden Mittelwerte bzgl. des mütterlichen Alters, des Gestationsalters bei der Geburt sowie der kindlichen Geburtsgewichte gebildet und einander zugeordnet (Tab. I).
Die Blutproben wurden direkt aus der Umbilikalarterie entnommen. Wir bestimmten das Gesamtbilirubin, Gesamtprotein und legten eine Elektrophorese an. Bei 38 gelb aussehenden Neugeborenen wurde schließlich während ihres gesamten Aufenthaltes auf der Station täglich das Gesamtbilirubin aus dem venösen Blut bestimmt. Hinsichtlich der Gesamtbilirubinwerte im Nabelschnurarterienblut fanden sich keine signifikanten Unterschiede zwischen den drei Gruppen. Die Gesamtproteinkonzentration war jedoch in Gruppe I höher als in den Gruppen II und III, wobei der Unterschied zwischen Gruppe I und III statistisch signifikant war ($p < 0.05$). Bilirubinspiegel, die über 208 µmol/l lagen, waren mit 33.3% in der Ocytocingruppe (Gruppe II) weitaus häufiger als in Gruppe I (6.8%) und Gruppe II (12.5%). Zwischen den Bilirubinmaxima von gelb erscheinenden Neugeborenen und ihrer Gesamtproteinkonzentration im Nabelschnurblut ließ sich keine signifikante Korrelation feststellen (Abb. 2).
Die Tatsache, daß sich keinerlei Abhängigkeit der Bilirubinwerte in der Nabelarterie vom Wehentyp (spontan bzw. induziert) und vom Geburtsverlauf zeigt, muß so gedeutet werden: unkonjugiertes Bilirubin gelangt über das Transportsystem in der Plazenta schon vor der Geburt in den mütterlichen Kreislauf. Die signifikant niedrigere Proteinkonzentration in der Sectiogruppe läßt sich auf die relative Unreifen der Feten, die ja vor dem spontanen Einsetzen der Geburt entbunden werden, zurückführen. In den Gruppen I und II ist der Reifezustand jedoch ähnlich. Das schließen wir zum einen daraus, daß sich die Wehen in Gruppe II relativ leicht zu induzieren ließen sowie aus den vergleichbaren Gesamtproteinkonzentrationen in beiden Gruppen. Trotzdem ist die neonatale Hyperbilirubinämie nach Oxytocingabe signifikant möglich.
Auf der anderen Seite besteht aber kein Zusammenhang zwischen einer operativen Entbindung und neonataler Gelbsucht, was in unserem Kontext gegen die fetale Unreife als Ursache der Hyperbilirubinämie spricht. **Vielmehr muß ein direkter Effekt des Ocytocins als Auslöser in Erwägung gezogen werden.**
Wir schließen aus unserer Untersuchung, daß ein bislang noch unbekannter Pharmakoneffekt für das verstärkte Auftreten von neonataler Gelbsucht nach ocytocininduzierten Wehen verantworlich zu machen ist. Die Folge ist eine längere Hospitalisierung der Neugeborenen.
Eine Ocytocingabe sollte daher nur bei ausreichender medizinischer Indikation erfolgen, wobei, da ja eine Dosisabhängigkeit besteht, die minimale effektive Dosis einzusetzen ist.

Schlüsselwörter: Hyperbilirubinämie, Nabelschnurblut, neonatale Gelbsucht, Ocytocin, Weheninduktion.

Resumé

Concentrations de bilirubine et de protéine dans le sang du cordon après travail spontané et induit. Correlation avec l'hyperbiliruinémie néonatale.
De nombreux travaux ont montré l'augmentation de la fréquence de l'ictère néonatal chez les nouveaux-nés après administration d'ocytocine pendant le travail. **La question de savoir si l'hyperbilirubinémie est le résultat de l'induction elle-même à la suite de la relative immaturité hépatique foetale ou bien d'un éventual effet de l'ocytocine, reste ouverte.**
Nous avons tenté d'apporter un peu de lumière dans cette question en mensurant les concentrations de bilirubine et

de protéine dans le sang cordonnal et en les mettant en rapport avec l'incidence de l'hyperbilirubinémie néonatale. Les investigations ont été réalisées chez 71 parturientes à terme choisies de façon randomisée, avec des grossesses normales et ayant accouché d'enfants normaux en bonne santé.

Les sujets ont été divisés en 3 groupes: le groupe 1 – accouchements normaux par voie vaginale après déclanchement spontané du travail (n = 42); groupe II – accochements normaux par voie vaginale après déclanchement du travail à l'ocytocine (n = 14); et groupe III – césariennes électives. Des groupes I et II nous avons retiré les valeurs moyennes d'âge maternel, d'âge de grossesse à l'accouchement et de poids des enfants à la naissance (Tableau I).

Le sang a été prélevé directement de l'artère ombilicale et analysé en ce qui concerne la bilirubinémie totale et la protéinémie totale. Nous avons également pratiqué des électrophorèses protéiques. Enfin nous avons dosé la bilirubinémie totale journellement dans le sang veineux de 38 nouveux-nés qui apparaissaient ictériques durant leur séjour dans le département de néonatologie.

Il n'a pas été noté de différence significative entre les valeurs moyennes de bilirubinémie totale dans le sérum de l'artère ombilicale dans les trois groupes. Par contre, la concentration moyenne de protéine était plus élevés dans le groupe I que dans les groupes II et III, la différence entre les groupes I et III étant statistiquement significative ($p < 0,05$). Des valeurs de bilirubine sérique supérieurs à 208 mmol/l survenaient dans 33.3% des cas du groupe ocytocine (Groupe II7, comparés aux seuls 6,8% et 12,5% des groupes I et III respectivement. Les bilirubinémies maximales chez les nouveaux-nés qui apparaissaient ictériques à la naissance n'offraient pas de corrélation significative aus protéinemies totales dans le sang cordonnal (fig. 2).

La corrélation entre la bilirubinémie sérique de l'artère ombilicale et le mode de début du travail et de voie d'accouchement peut s'expliquer par le transfer déja existant de bilirubine non conjuguée à travers le placenta du sang foetal vers la circulation maternelle avant la naissance. Les concentrations de protéine totale significativement plus basses dans le «groupe des césariennes» peut être expliquée par la relative immaturité des foetus nés avant la date du déclenchement spontané du travail. La facilité du succès de l'induction dans le «groupe ocytocine» implique peut-être une maturité foetale comparable à celle trouvée dans le «groupe à accouchement spontané», comme le confirment les concentrations similaires de protéines dans ces groupes. Malgrè celà, l'hyperbilirubinémie néonatale était beucoup plus fréquente après travail induit par l'ocytocine.

Il n'a pas été noté d'association similaire entre les césariennes électives et l'ictère néonatal, ce qui apparamment infirme **la conception de l'immaturité foetale dans ce contexte et implique un effet direct de l'ocytocine comme cause d'hyperbilirubinémie.**

Notre étude montre que l'administration d'ocytocine entraine par un mécanisme non encore éllucidé une augmentation de la fréquence de l'ictère néonatal, impliquant une hospitalisation prolongée.

Ceci prouve que l'ocytocine n'est à appliquer que si médicalement nécéssaire et, mise à part la possibilité de dépendance des doses, la dose minimale éffective devrait être utilisée.

Mots-clés: Déclenchement du travail, hyperbilirubinémie, ictère néonatal, ocytocine, sans du cordon.

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